NEW DRUG APPROVAL

Brand Name	Zynlonta™
Generic Name	loncastuximab tesirine-lpyl
Drug Manufacturer	ADC Therapeutics

New Drug Approval

FDA Approval Date: April 23, 2021

Review Designation: N/A, Orphan

Type of Review: Biological Licence Application (BLA) 761196

Dispensing Restrictions: Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non−Hodgkin lymphoma (NHL) in the United States. About 1 out of every 3 lymphomas is DLBCL. It can affect people of any age, but the average age at the time of diagnosis is mid-60s. According to the National Cancer Institute (NCI), between 2014 and 2018, the rate of new cases of DLBCL was 5.6 per 100,000 men and women per year. The death rate was 1.8 per 100,000 men and women per year.

DLBCL usually starts as a fast-growing (aggressive) mass in a lymph node deep inside the body, such as in the chest or abdomen, or in a lymph node in the neck or armpit, but it can also start in other areas such as the intestines, bones, brain, or spinal cord. DLBCL is curable in approximately 50% of patients with current frontline therapy, but patients who relapse or are refractory to frontline management have a poor prognosis.

Efficacy

The efficacy of Zynlonta™ was evaluated in LOTIS-2 (NCT03589469), an open-label, single-arm trial in 145 adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after at least 2 prior systemic regimens. The trial excluded patients with bulky disease and active central nervous system lymphoma. Patients received Zynlonta™ 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease, or unacceptable toxicity.

Efficacy was established on the basis of overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria (Table below). The median follow up time was 7.3 months (range 0.3 to 20.2)

Efficacy Results in Patients with Relapsed or Refractory DLBCL	
Efficacy Parameter	**Zynlonta™ (N = 145)**
Overall response rate by IRC[a] , (95% CI)	48.3% (39.9, 56.7)
Complete response rate (95% CI) Partial response rate (95% CI)	24.1% (17.4, 31.9) 24.1% (17.4, 31.9)
Duration of overall response[b]	**N = 70**
Median (95% CI), months	10.3 (6.9, NE)

CI = confidence interval, NE = not estimable

[a] IRC = independent review committee using Lugano 2014 criteria

[b] Of 70 patients with objective response, 25 (36%) were censored prior to 3 months. Twenty- six percent of responders had a duration of response ≥ 6 months

The median time to response was 1.3 months (range 1.1 to 8.1).

Safety

ADVERSE EVENTS

Most common (≥20%) adverse reactions, including laboratory abnormalities, are thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

WARNINGS & PRECAUTIONS

- Effusion and Edema: Serious effusion and edema occurred in patients treated with Zynlonta™. Monitor for the development of pleural effusion, pericardial effusion, ascites, peripheral edema, and general edema. Consider diagnostic imaging when symptoms develop or worsen.
- Myelosuppression: Treatment with Zynlonta™ can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Monitor blood cell counts. Withhold, reduce, or discontinue Zynlonta™ based on severity.
- Infections: Fatal and serious infections, including opportunistic infections, occurred in patients treated with Zynlonta™. Monitor for infection and treat promptly.
- Cutaneous Reactions: Serious cutaneous reactions occurred in patients treated with Zynlonta™. Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Dermatologic consultation should be considered.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Loncastuximab tesirine-lpyl is an antibody-drug conjugate (ADC) targeting CD19. The monoclonal IgG1 kappa antibody component binds to human CD19, a transmembrane protein expressed on the surface of cells of B-lineage origin. The small molecule component is SG3199, a PBD dimer and alkylating agent.

Dose & Administration

ADULTS

Zynlonta™ as an intravenous infusion administered over 30 minutes on Day 1 of each cycle (every 3 weeks). Administer intravenous infusion as follows:

- 0.15 mg/kg every 3 weeks for 2 cycles.
- 0.075 mg/kg every 3 weeks for subsequent cycles.

Recommended Premedication: Unless contraindicated, administer dexamethasone 4 mg orally or intravenously twice daily for 3 days beginning the day before administering Zynlonta™. If dexamethasone administration does not begin the day before Zynlonta™, dexamethasone should begin at least 2 hours prior to administration of Zynlonta™.

PEDIATRICS

Safety and effectiveness of Zynlonta™ in pediatric patients have not been established.

GERIATRICS

No overall differences in safety or effectiveness were observed between geriatric patients and younger patients.

RENAL IMPAIRMENT

- Mild to moderate renal impairment**:** There are no dosage adjustments provided in the manufacturer's labelling; however, loncastuximab tesirine has minimal renal excretion and CrCl 30 to 89 mL/minute had no clinically significant difference on loncastuximab tesirine pharmacokinetics.
- Severe renal impairment/end stage renal disease: There are no dosage adjustments provided in the manufacturer's labelling.

HEPATIC IMPAIRMENT

- Mild hepatic impairment: No dose adjustment is recommended.
- Moderate or Severe hepatic impairment: Zynlonta™ has not been studied in patients with moderate or severe hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

For injection: 10 mg of loncastuximab tesirine-lpyl as a lyophilized powder in a single-dose vial for reconstitution and further dilution.